Attachment 3: Revised Toxicology Chapter

MEMORANDUM

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Chemical: Methyl Parathion
Case #
Pesticide Chemical Code 053501
CAS Reg No. 298-00-0

Attached is the Toxicology Chapter for the Methyl Parathion RED

1. Toxicology Data Base

The toxicological data base on Methyl Parathion is **complete, pending submission of a developmental neurotoxicity study,** and will support reregistration eligibility.

a. Acute Toxicity

The following table summarizes the acute toxicity data for methyl parathion.

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral (rat)		LD_{50} = 4.5-24 mg/kg	I
81-2	Acute Dermal (rat)		$LD_{50=}$ 6 mg/kg	I
81-3	Acute Inhalation (rat)	256961	LC_{50} <0.163 mg/L	I
81-4	Primary Eye Irritation	256966, 40542602	Irritation clear by 7 days	III
81-5	Primary Skin Irritation	256962	Max. score=2.0; 72 h=0.5	IV
81-6	Dermal Sensitization	256963	Negative	
81-8	Acute Neurotoxicity Delayed Hen	41606801	Negative	--

In an acute inhalation toxicity study (MRID No. 40364103), Albino rats (Sprague-Dawley descended, 5/sex/group) were exposed to Methyl Parathion 80% Technical by inhalation (nose-only) for 4 h at concentrations of 0.108, 0.134, or 0.168 mg/liter. Mortality was 2 males (at 98 min. exposure) for the 0.108 mg/l group, 3 males (at 120-129 min. exposure) for the 0.134 mg/l group, and 5 males and 4 females (at 43-96 min. exposure) for the 0.168 mg/l group. During exposure, all animals showed respiratory depression and salivation. All surviving animals showed clinical signs at the end of exposure, including: subdued or inactive behavior, respiratory depression, body tremors, unkempt condition. Males also showed labored respiration. One animal in the 0.108 mg/l group had an opacity in the left eye on days 2-10 post-exposure. By day 5, all surviving animals in the 0.108 mg/l group were considered normal. The surviving animals in the 0.134 mg/l group were normal by day 4. The one surviving animal in the 0.168 mg/l group continued to show unkempt condition until day 9, and was normal thereafter. In addition, all surviving animals had body weight loss, which was regained by day 10; overall body weight gain was still considered lower than expected on day 14. The 4 h LC50 for methyl parathion 80% technical was calculated to be 0.135 mg/l (95% confidence limits 0.145-0.125 mg/l). A NOEL could not be determined for this study, because all exposed animals displayed toxic signs (weight loss, respiratory depression, salivation, body tremors, and unkempt appearance). NOEL for inhalation exposure is <0.108 mg/l. The study is classified as tentatively acceptable.

In a second acute inhalation study (MRID No. 142803), Albino rats (strain Hsd:(SD) BR), 5/sex/group, were exposed by inhalation to Methyl Parathion Technical (purity, composition, and stability not provided) as follows: 0.163 mg/l for 4 hours, or 1.06 mg/l for 1.5 h. All animals died during the study. Necropsy findings included discoloration of lungs, lungs edematous, adrenal glands enlarged, corneal opacity, and changes in the gastrointestinal tract. Clinical observations

included decreased activity, body tremors, chromodacryorrhea, convulsions, constricted pupils, labored breathing, salivation, lacrimation, piloerection, etc. No NOEL could be determined based on this study. All animals demonstrated cholinergic signs and died prior to completion of study. The LC50 for methyl parathion technical is <0.163 mg/l. The study is classified as tentatively acceptable.

b. Subchronic Toxicity

Available studies are adequate to satisfy subchronic testing requirements for this chemical.

Subchronic toxicity in mice

In a three month feeding study in mice (MRID No. 72513), Methyl parathion (purity 93.7%) was administered to mice (15/sex/group) in the diet at 0, 10, 30, or 60 ppm (approximately 0, 2.1, 6.5, 13.5 mg/kg/day for males; 0, 2.5, 8.6, 16.2 mg/kg/day for females, respectively) for 90 days. There was a significant decrease in body weight of high dose males throughout the study (4-20% less than controls; body weight was 94% of controls at study termination). Absolute brain weights of high dose males and females were slightly increased (significant increase in brain/body weight ratio for high dose males only). Testes weights of all treated males were decreased in a dose-related manner (significant only as testes/brain weight ratio in high dose males). Ovary weights of mid and high dose females were slightly decreased (significant only as ovary/brain weight ratio in high dose females). There were no compound-related histopathological findings (peripheral nerve was not microscopically examined). The systemic LOEL is 60 ppm (13.5 mg/kg/day for males, 16.2 mg/kg/day for females), based on decreased body weight in males and decreased testes/brain weight ratio; decreased ovary/brain weight ratio in females. The systemic NOEL is 30 ppm (6.5 mg/kg/day for males, 8.6 mg/kg/day for females).

This nonguideline [82-1] subchronic feeding study in mice is classified as Acceptable, although cholinesterase inhibition, clinical chemistry, and hematology were not measured, and histopathological evaluation was limited. There is a long-term [carcinogenicity] study in the mouse available.

Subchronic toxicity in rats

In a three month feeding study in rats (MRID No. 74299), Methyl parathion (purity 93.7%) was administered to Sprague-Dawley CD rats (20/sex/group) in the diet at 0, 2.5, 25, or 75 ppm for three months (mean daily intake, corrected for compound stability, was approximately 0.12, 1.24, 4.46 mg/kg/day for males, 0.16, 1.55, 5.15 mg/kg/day for females, respectively). In the high dose group, 14 females and 1 male died or were sacrificed (due to extreme morbidity) during the first 4 weeks of study. The study report stated that all high dose females and some high dose males exhibited tremors and emaciation (data not provided). The following additional effects were found: significantly reduced body weight at all time points (high dose males (16-23% less than controls) and females (24-35% less than controls); increased food consumption (significant at week 4 and all subsequent weeks, high dose males (18-37% greater) and females (12-30% greater); significantly decreased hemoglobin (mid- and high dose males, high dose females),

hematocrit (high dose males and females), and red blood cell count (high dose females); changes in several clinical chemistry parameters, including increased alkaline phosphatase (high dose males and mid- and high dose females), increased SGOT (high dose females), increased BUN (high dose females), decreased glucose (high dose males and females), decreased total protein (high dose males and females), decreased albumin (high dose males), decreased globulin (high dose males and females), increased A/G ratio (mid and high dose males, females at all dose levels); apparently increased specific gravity in urinalysis (high dose males and females; note that neither statistical analysis nor summary data were provided in the report).

Plasma cholinesterase was significantly inhibited in high dose males (9-27%) and in the mid- and high doses for females (29-39% and 54-68%, respectively); RBC cholinesterase was significantly inhibited in mid, and high dose males (41-43%, and 9-48%, respectively) and mid and high dose females (33-48% and 31-63%, respectively). At 3 months, brain cholinesterase was significantly inhibited in mid- and high dose females (32% and 81%, respectively) and in high dose males (74%).

Absolute organ weights were decreased in high dose males (heart, kidneys, and liver) and females (ovaries, heart, and liver). Relative organ/body weights were increased in high dose males (brain, testes, heart, kidneys) and females (brain, ovaries, heart, kidneys). These changes were probably due, at least in part, to decreased body weight in high dose animals.

Apparently treatment-related histopathological lesions included (results refer to high dose groups unless otherwise noted): acute gastritis, acanthosis and hyperkeratosis in the cardia (stomach, mid- and high dose males and females), focal tubular regeneration in the kidneys (males), posterior synechia (eye, female), lymphocytic necrosis and lymphocytic depletion (spleen, female), cellular necrosis (salivary gland, female), lung congestion (female), lymphocytic necrosis (thymus, female), liver congestion (female), hypocellularity (bone marrow, female). Note that, since 14 of the high dose females died after less than 4 weeks of exposure, histopathological results may not be comparable between this group and the other groups.

Based on the results of this study, the LOEL for systemic effects (hematological changes, stomach lesions) was 25 ppm (1.24 mg/kg/day for males, 1.55 mg/kg/day for females), and the NOEL for systemic effects was 2.5 ppm (0.16 mg/kg/day for males, 0.12 mg/kg/day for females). The LOEL for cholinesterase inhibition (brain, plasma, and erythrocyte) was established at 25 ppm (1.24 mg/kg/day for males, 1.55 mg/kg/day for females), the NOEL was 2.5 ppm (0.16 mg/kg/day for males, 0.12 mg/kg/day for females).

This guideline [82-1] study was classified as Acceptable.

Subchronic toxicity in dogs

In a ninety day feeding study in dogs (MRID No. 72512), Methyl parathion (purity 94.3%) was administered in diet to beagle dogs (4/sex/group) at 0, 0.3, 1.0, and 3.0 mg/kg/day for 90 days. No differences between control and treated animals were found with respect to food consumption, body weight gain, or clinical signs. Pulse rate was significantly decreased at 13

weeks for high dose females only (control rate was 161, high dose females was 121). No biologically relevant effects were found on clinical chemistry parameters or hematological parameters (scattered significant effects were not dose-related or consistent across time). No treatment-related effects were seen on analysis of urine samples. No treatment-related effects were seen on organ weights, or histopathologically.

Plasma cholinesterase activity was significantly decreased in mid-dose males at 13 weeks (72% of control) and in high dose males and females at 6 and 13 weeks (37-53% of control). RBC cholinesterase activities were significantly decreased in high dose males and females at 6 and 13 weeks (23-34% of control), and in mid-dose males and females at 13 weeks (63-64% of control). Brain cholinesterase activity was significantly decreased in high dose males and females at 13 weeks (the only time point measured; 36-44% of control).

Based on the results of this study, the LOEL for cholinesterase inhibition (plasma and RBC), was established at 1.0 mg/kg/day; the NOEL was established at 0.3 mg/kg/day. The LOEL for brain cholinesterase inhibition was 3.0 mg/kg/day; the NOEL was established at 1.0 mg/kg/day. For systemic effects (decreased pulse rate in females), the LOEL was 3.0 mg/kg/day, with a NOEL of 1.0 mg/kg/day.

This guideline [82-1] study was classified as Acceptable.

Dermal toxicity in rabbits

In a 21-day dermal study in rabbits (MRID No. 42263701), Methyl parathion was evaluated at dosages of 0 (vehicle control, 1% carboxymethylcellulose), 1, 5, 10, and 100 mg/kg/day. There were no mortalities or clinical signs of toxicity during the study. No adverse effects were apparent based on body weight, body weight gain, food consumption, clinical pathology parameters or organ weights. Histopathologic evaluations of the kidneys, liver and skin from high-dose rabbits did not reveal any treatment-related effects. Treatment-related RBC cholinesterase inhibition was seen in 10 and 100 mg/kg/day males and females.

No dermal effects were seen in treated males, however, slight erythema and edema was induced in 1, 5, and 10 mg/kg/day females; one 10 mg/kg/day female also had slight fissuring. The severity of these reactions did not increase with dosage. No dermal reactions were reported in 100 mg/kg/day females. Although no dermal effects were seen in treated males, the noted effects in females obviate the establishment of a NOEL for local dermal toxicity in this study.

The LOEL for systemic toxicity was 10 mg/kg/day based on RBC cholinesterase inhibition in both sexes and the NOEL was 5 mg/kg/day under the conditions of this study. A definitive NOEL for local dermal toxicity could not be determined in this study.

This guideline [82-2] study was rated Acceptable.

c. Chronic Toxicity and Carcinogenicity

Available studies are adequate to satisfy chronic toxicity and carcinogenicity testing requirements for this chemical.

Chronic toxicity in dogs

In a one-year study in dogs (MRID No. 93895), Purebred beagle dogs (8/sex/group) were administered methyl parathion (purity 93.7%) in the diet at 0, 0.03, 0.1, or 0.3 mg/kg body weight/day. Plasma and RBC cholinesterase activity were sporadically (significantly) depressed at all dose levels, at different time points. The decreases were not always dose-related, but the variance was high. At 12 months, RBC cholinesterase was significantly decreased at all dose levels for both sexes (males: 68-81% of control; females: 71-78% of control). Plasma cholinesterase levels in treated animals ranged from 66-83% of control for males, 52-81% of control for females. Brain cholinesterase was not significantly depressed at any dose level (it was significantly increased in high dose males), but again the variance was very high.

There was no compound-related effect on body weight, feed consumption, urinalysis, clinical chemistry, or histological findings. Absolute liver weights were slightly, but significantly, increased in high dose males; in the absence of body weight changes, liver specific enzyme changes, or histopathology this effect was not considered toxicologically significant. No treatment-associated clinical signs were reported, but the clinical observations were not included in the report.

Based on the results of this study, the LOEL for RBC and plasma cholinesterase inhibition was established at 0.03 mg/kg/day; the NOEL for cholinesterase inhibition was not established. The LOEL for brain cholinesterase inhibition was established at $\geq$ 0.3 mg/kg/day, the NOEL was established at 0.3 mg/kg/day. For systemic effects, the LOEL was $\geq$ 0.3 mg/kg/day, the NOEL was 0.3 mg/kg/day.

This study was classified as Unacceptable and does not satisfy guideline requirements by itself, but was upgraded to acceptable upon submission of the 90-day dog bridging study.

In a subchronic bridging study in dogs (MRID No. 413354-01), Beagle dogs (8/sex/group, 4 of which were sacrificed after a 4-week recovery period) were treated with methyl parathion (purity 94.9%) in the diet at 0, 0.03, 0.3, or 3.0 mg/kg/day for 13 weeks. Two high dose males exhibited emaciation, dehydration, and thin appearance from study weeks 11-13, one low-dose male appeared thin from weeks 9-13 and throughout recovery period. Mean body weight gains of high dose males and females were depressed throughout dosing period (31% of control for males, 66% of control for females), with no change in food consumption. No treatment-related effects were seen in the ophthalmological examinations or ocular histopathology.

Plasma and erythrocyte cholinesterase were depressed in high dose males and females at weeks 6 and 13 (the decrease was significant except for males (erythrocyte) at week 13), but not at week 17 (recovery). Plasma cholinesterase inhibition ranged from 47-59%, erythrocyte inhibition ranged from 18-23%. Brain cholinesterase (pons and cerebellum) was significantly inhibited in high dose males and females at week 13 (43-55% inhibition), but not at week 17 (recovery).

Based on the results of this study (decrease in weight gain), the systemic LOEL was established at 3.0 mg/kg/day; the systemic NOEL was established at 0.3 mg/kg/day. For cholinesterase inhibition (brain, plasma, and erythrocyte), the LOEL was 3.0 mg/kg/day, the NOEL was 0.3 mg/kg/day.

This study is classified as Acceptable and does not satisfy guideline requirements for a subchronic study in dogs. This study includes bridging data which allow the classification of the 1 year chronic feeding study in dogs to be upgraded to Acceptable (Guideline 83-1).

An additional non-guideline, chronic dog study was submitted during the comment period (MRID 44674201). Methyl parathion (purity 96.5%) was administered to dogs in the diet at 0.3, 1.0, 3.0, 3.5, or 4.5 mg/kg/day for up to one year. Preliminary review indicates the results of this study will not change the risk assessment.

Chronic toxicity/carcinogenicity in rats

In a chronic toxicity/carcinogenicity study in rats (Accession Nos. 257513, 257514), Methyl parathion (purity 94.8%) was administered to Wistar rats (50/sex/group for treatment groups, 100/sex/group for controls) at doses of 0, 2, 10, or 50 ppm (approximately 0.09, 0.46, 2.6 mg/kg/day for males, 0.14, 0.71, and 4.97 mg/kg/day for females, respectively) for 2 years. Interim sacrifices of an additional 10 animals/sex/group were performed at 6 and 12 months.

Cholinergic symptoms were observed in some high dose animals, and 9 animals in the high dose group (3M, 6F) died in the first two weeks of the study. Body weights were significantly decreased in high dose animals only, food consumption was increased in high dose females. Hemoglobin and hematocrit were slightly but significantly decreased in high dose males and females at 24 months; reticulocyte counts were significantly increased in high dose males and females at 6 months and in high dose females at 24 months. Urinary protein was increased in 50 ppm females (significantly at 1 and 6 months). Serum protein was significantly decreased in high dose females at all time points. Brain cholinesterase was significantly decreased in both sexes at 50 ppm (37% of control for females, 50% of control for males), and in males at 10 ppm (78% of control). Erythrocyte cholinesterase was significantly decreased at all time points, both sexes, at 50 ppm (58-79% of control), all time points except week 1, both sexes, at 10 ppm (73-83% of control), and sporadically at 2 ppm (week 13 for females only, week 52 for both sexes; 83-89% of controls). Plasma cholinesterase was significantly decreased at all time points, both sexes at 50 ppm (9-41% of controls) and sporadically in both sexes at 10 ppm (61-111% of controls).

Significant decreases in organ weight at 2 years in the high dose group (heart, lung, liver, spleen, kidney for males and females, adrenal for males only) were probably due to decreases in body weight; relative organ/body weight ratios did not vary among groups. Slight increases in incidences of thyroid adenomas, pituitary adenomas, Leydig cell tumors, and uterine adenocarcinomas were found not to be biologically significant. Non-neoplastic lesions included an increase in PAS-positive material in cortical tubules of the kidney in 2 and 10 ppm groups only, and an increase in ORO-positive material in hepatocytoplasm of 10 ppm and 50 ppm males.

Based on the results of this study (liver histopathology), the LOEL for systemic effects was established at 10 ppm (0.46 mg/kg/day for males, 0.71 mg/kg/day in females); the NOEL was established at 2 ppm (0.09 mg/kg/day for males, 0.14 mg/kg/day for females). There was no indication that methyl parathion induced neoplastic lesions. For cholinesterase inhibition (brain, plasma and RBC in both sexes), the LOEL was established at 10 ppm (0.46 mg/kg/day for males, 0.71 mg/kg/day in females); the NOEL was established at 2 ppm (0.09 mg/kg/day for males, 0.14 mg/kg/day for females).

This study is classified as Acceptable for carcinogenicity ([Guideline 83-2] classification upgraded following submission of supplementary information) and Unacceptable for chronic toxicity (due to inadequate presentation of clinical data, lack of ophthalmic observations, insufficient numbers of animals used for clinical laboratory studies and cholinesterase determinations, and other deficiencies).

In a second chronic toxicity/carcinogenicity study in rats (Acc. No. 252501, 252502, 252503, 253346, 253372, 253373, 253374), Methyl Parathion (purity 93.7%) was administered to Sprague Dawley rats (60/sex/group) at 0, 0.5, 5, and 50 ppm in the diet (mean compound intake approximately 0, 0.02, 0.21, and 2.21 mg/kg/day for males and 0, 0.03, 0.29, and 3.34 for females) for 26 (males) or 28 (females) months.

Effects seen at the 5.0 ppm dose were abnormal gait in one female, significant decreases in hematocrit and erythrocyte levels in males at 24 months, slight decreases in erythrocyte cholinesterase activity in both sexes (+4.4 to -11.3% inhibition). Additional effects seen at 50 ppm were significant decreases in hemoglobin, hematocrit, and erythrocyte levels in females (at all time points), significant decreases in activity of plasma (67-89% inhibition), erythrocyte (0-20% inhibition), and brain cholinesterase (76-79% inhibition) at multiple time points (males and females), increased incidence of alopecia (more pronounced in females), bilateral retinal degeneration and posterior subcapsular cataract (females only, at 24 months), decreased mean body weight and increased food consumption (both sexes), irritability (both sexes), tremors (largely in females), increased incidence of ano-genital staining, decreased incidence of chromodacryorrhea, and soft stools. There was also a slight apparent increase in survival in 50 ppm females.

Neurological changes (in particular sciatic nerve degeneration) were most pronounced in animals receiving 50 ppm, but lesions in low and mid-dose males were slightly more severe than those seen in control animals.

No oncogenic effects were seen at 50 ppm (highest dose) in either sex. Doses were considered adequate to test for carcinogenicity.

The LOEL for neurological effects in this study, based on increases in lesion severity (sciatic nerve degeneration, males) was established at 5.0 ppm (0.21 mg/kg/day in males, 0.29 mg/kg/day in females); the NOEL was established at 0.5 ppm (0.02 mg/kg/day for males, 0.03 mg/kg/day for females). Based on other effects seen in this study (decreased hematocrit and erythrocyte levels), the systemic LOEL was established at 5.0 ppm (0.21 mg/kg/day in males, 0.29 mg/kg/day in females); the NOEL was established at 0.5 ppm (0.02 mg/kg/day in males, 0.03 mg/kg/day in females). The LOEL for cholinesterase inhibition (decreased erythrocyte cholinesterase activity in both sexes) was established at 5.0 ppm (0.21 mg/kg/day in males, 0.29 mg/kg/day in females); the NOEL was established at 0.5 ppm (0.02 mg/kg/day in males, 0.03 mg/kg/day in females).

This study [Guideline 83-2] is classified as Acceptable for oncogenicity and Acceptable for chronic toxicity.

Chronic toxicity/carcinogenicity in mice

In a chronic toxicity/carcinogenicity study in mice (MRID No. 42216401), Methyl parathion (purity 95.5%) was administered in diet to mice (50/sex/group in main 2 year study, 15/sex/group in the 12 month satellite study) at levels of 0, 1, 7, and 50 ppm (mean intakes of 0, 0.2, 1.6, and 9.2 mg/kg/day in males; 0, 0.3, 2.1, and 13.7 mg/kg/day in females) for 2 years.

There was no dose-related difference in survival among groups. Body weights were significantly increased in the high dose groups of both sexes (107-119% of control), overall food consumption was decreased in these groups. No treatment-related effect was found on hematology parameters; serum cholesterol levels were significantly increased in 50 ppm males at 12 months and in 7 and 50 ppm females at 24 months. Plasma cholinesterase was significantly decreased at 50 ppm in both males (71-75% inhibited) and females (62-65% inhibited) at 12 and 24 months; erythrocyte and brain cholinesterase were significantly decreased for 7 and 50 ppm groups in both males and females at 12 and 24 months (erythrocyte ChE: 41-57% inhibited at 7 ppm, 76-89% inhibited at 50 ppm; brain ChE: 0.6-37% inhibited at 7 ppm; 46-85% inhibited at 50 ppm).

Slight increases in absolute liver and kidney weights were seen at 12 or 24 month sacrifices, high dose males and females only. An increase in adipose tissue was also found in high dose males and females at study termination. Histopathological examination found no neoplastic or nonneoplastic changes related to treatment in either sex (non-neoplastic findings were attributed to age).

Based on the results of this study, the LOEL for systemic effects was established at 7 ppm (increased serum cholesterol levels in females) (1.6 mg/kg/day for males, 2.1 mg/kg/day for females), and the systemic NOEL was established at 1 ppm (0.2 mg/kg/day for males, 0.3 mg/kg/day for females). The LOEL for cholinesterase inhibition (brain and erythrocyte cholinesterase inhibition) was established at 7 ppm (1.6 mg/kg/day in males, 2.1 mg/kg/day in females); the NOEL was established at 1 ppm (0.2 mg/kg/day in males, 0.3 mg/kg/day in females). There was no treatment-related increase in tumors in either sex.

This guideline [83-2] carcinogenicity study in mice is classified as Acceptable.

d. Developmental Toxicity

Available developmental toxicity studies are adequate to satisfy guideline requirements, however the Committee determined the need for a developmental neurotoxicity study (see below).

<u>Developmental toxicity in rats</u>

In a developmental study in rats (MRID No. 41136101), Methyl parathion (purity 97%) at 0, 0.3, 1.0, and 3.0 mg/kg/day was administered by oral gavage (in water mixed with Cremophor EL) to female pregnant Wistar/HAN rats (25/group, main group) from days 6 through 15 of gestation. An additional 10 rats (subgroup) at 0 and 3.0 mg/kg/day were similarly treated and sacrificed on day 16 of gestation for determination of plasma, erythrocyte, and brain cholinesterase inhibition.

Signs of maternal toxicity were seen in high dose only, including mortality (5 maternal deaths), decreased body weight, body weight gain, and food consumption, and increased clinical signs. In the 3.0 mg/kg/day subgroup, plasma, red blood cell, and brain cholinesterase activities were significantly decreased (59%, 29%, and 78% of control levels, respectively); cholinesterase inhibition was not measured in lower dose groups or in fetal tissue.

Developmental toxicity was also seen only in the high dose group: increased post-implantation

loss and embryonic resorptions, decreased group mean fetal body weight and litter mean body weight, and an increase in delayed ossification.

Based on the results of this study (decreased maternal weight gain and clinical signs), the maternal LOEL was established at 3.0 mg/kg/day, the maternal NOEL was 1.0 mg/kg/day; the developmental LOEL (based on increased post-implantation loss, embryonic resorptions, and decreased fetal weight) was established at 3.0 mg/kg/day, the developmental NOEL was established at 1.0 mg/kg/day. Cholinesterase inhibition was demonstrated at 3.0 mg/kg/day, but was not measured at lower doses, so no NOEL for that effect can be established.

This study is classified as Acceptable-Guideline [83-3].

Developmental toxicity in rabbits

In a developmental toxicity study in rabbits (MRID No. unknown), Methyl parathion (purity 95.7%) was administered orally, by gavage, to 15 mated female Himalayan rabbits (strain CHBB:HM), on days 6-18 of gestation at 0, 0.3, 1.0, and 3.0 mg/kg. The study was terminated on day 29.

No toxic signs or changes in maternal weight gain related to treatment were observed in the dams during gestation. Fetal and placental weights were comparable across treatment groups. No treatment-related effects on any measured parameter were observed in the fetuses.

Supplementary data (MRID No. 41046101) subsequently documented inhibition of plasma and RBC cholinesterase on gestation day 14 (9.3% and 24.8% inhibited, respectively) and gestation day 19 (12.5% and 19.5% inhibited, respectively) in mated females at the 3.0 mg/kg/day dose (statistically significant in RBC, only). Brain cholinesterase was not inhibited in any treatment group (112% of control on day 19 for 3.0 mg/kg/day dose group).

Based on the results of this study, the maternal LOEL for cholinesterase inhibition (plasma and RBC cholinesterase inhibition) was established at 3.0 mg/kg/day; the NOEL was established at 1.0 mg/kg. The developmental LOEL was >3.0 mg/kg/day, with a NOEL of 3.0 mg/kg/day. Maternal systemic NOEL was >3.0 mg/kg/day.

This study was classified as Acceptable-Guideline [83-3].

An additional guideline developmental study in rabbits was submitted during the comment period (MRID 44691004). Methyl parathion (purity 95.7%) was administered by gavage at doses of 0, 0.3, 3, or 9 mg/kg to artificially inseminated rabbits on gestation days 6-18. Preliminary review indicates that no developmental effects were seen at any dose. In does, RBC cholinesterase inhibition was seen at all doses, and plasma cholinesterase inhibition was seen at 9 mg/kg (measured in does at 2 h post-dosing on gestation day 18). Cholinesterase inhibition was not measured in pups. Preliminary review indicates that the results of this study will not change the risk assessment.

e. Reproductive Toxicity

Available studies are adequate to satisfy the guideline requirements for reproductive toxicity testing, but the Committee determined the need for developmental neurotoxicity testing (see below).

Reproductive toxicity in rats

In a two-generation reproduction study in rats (MRID No. 00119087), Methyl parathion (purity 93.7%) was administered in the diet at 0, 0.5, 5.0, and 25 ppm to CD rats (30 females and 15 males per dose group) (mean compound intake approximately 0.04, 0.38, 2.0 mg/kg/day for males, 0.04, 0.44, and 2.3 mg/kg/day for females, respectively). Treatment was begun at age 6 weeks for F0 rats and continued throughout mating/gestation, and lactation. F0 rats were sacrificed at weaning of F1, at which time the F1 parental rats were selected (remaining F1 weanlings were sacrificed) and treatment was continued throughout growth, mating/gestation, and lactation. F1 parents were sacrificed 30 days after weaning of F2 pups, and F2 pups were sacrificed at weaning.

No treatment-related histopathological effects were found, nor were there any significant effects on reproductive parameters, except for maternal weight gain during lactation. Body weight gain of F0 and F1 females was significantly decreased during lactation, for the 25 ppm group only (gain was 19 g for control; at 25 ppm gain was -3 g for F0, and -7 g for F1). Body weight of F1 females receiving 25 ppm methyl parathion was significantly lower than that of control females for approximately 2 months post-weaning (89-93% of control), while food intake was consistently increased (107-121% of control; significantly increased on multiple occasions) during that same period. At the start of gestation, body weight was no longer significantly depressed, but maternal weight gain during lactation was significantly decreased for the 25 ppm treatment group only, starting on lactation day 14. In addition, there was a significant decrease in survival of F2 pups in the 25 ppm treatment group, from postnatal day 0 to postnatal day 4.

Based on the results of this study, the LOEL for reproductive and developmental effects (decreased pup survival) was established at 25 ppm (2.0 mg/kg/day for males, 2.3 mg/kg/day for females); the NOEL was established at 5 ppm (0.38 mg/kg/day for males, 0.44 mg/kg/day for females). The LOEL for parental (systemic) toxicity (decreased body weight gains during lactation and post-weaning) was established at 25 ppm (2.0 mg/kg/day for males, 2.3 mg/kg/day for females); the NOEL was established at 5 ppm (0.38 mg/kg/day for males, 0.44 mg/kg/day for females). Cholinesterase inhibition was not measured in this study.

This study is classified as Acceptable-Guideline [83-4].

f. Mutagenicity

Seven studies sponsored by the USEPA under contract Nos. 68-02-2947 or EPA-600/1-7-028 were available for review. Summaries of the acceptable studies (with MRID/Accession and/or Document Control Numbers) follow:

Gene Mutations

1) Salmonella typhimurium reverse gene mutation assay (MRID No. 00124901; Doc. No. 005095): The test is negative in S. typhimurium strains TA1535, TA1537, TA1538 and TA100 up to 1000 µg/plate +/-S9, the highest dose tested (HDT). Due to the lack of cytotoxicity at the HDT and other technical deficiencies, the study was classified as Unacceptable. However, the standard protocol used in this assay required testing up to 10,000 µg/plate +/-S9, unless solubility or cytotoxic prevent testing up to this level. The Committee, therefore, concluded that methyl parathion was assayed up to an appropriate high dose and found to be negative. It was further concluded that the assay should be upgraded.

2) Escherichia coli reverse gene mutation assay (MRID No. 00124901; Doc. No. 005095): The test is negative in E. coli WP2 up to the HDT (1000 µg/plate +/-S9). Due to the lack of cytotoxicity at the HDT and other technical deficiencies, the study was classified as Unacceptable. For reasons similar to those stated above, the Committee concluded that the assay should be upgraded.

3) Saccharomyces cerevisiae D7 reverse gene mutation, mitotic gene conversion and mitotic crossing-over assay (MRID No. 00132949; Doc. No. 005095): Independent test are negative at all three endpoints up to severely cytotoxic levels (≥1.0% +/-S9, equivalent to ≈10,000 µg/mL).

4) L5178Y TK $^{+/-}$ mouse lymphoma cell forward gene mutation assay (MRID No. not available; Doc. No. 005095/005588): Confirmed positive; dose-related mutagenic effects at 80-200 µg/mL with S9 activation. Positive responses were also seen in the absence of S9 activation; however, the effect was not clearly dose-related and reproducible increases in the mutation frequency were only seen at ≥150 µg/mL. (Colony sizing was not performed).

Chromosome Aberrations

5) Mouse Dominant lethal assay (MRID No. 00124901; Doc. Nos. 005095/005588): The test is negative in the germinal cells of male ICR/SIM mice receiving dietary administrations of 0, 20, 40 or 80 ppm methyl parathion for 7 weeks. No overt toxicity or cytotoxicity to the target organ occurred at the HDT. It was noted, however, that body weight reductions (4-20%) were seen at all weeks in males mice receiving dietary levels of 10, 30 or 60 ppm methyl parathion in the subchronic mouse study conducted with methyl parathion (MRID No. 00072513). Based on these findings, the Committee concluded that dosing was adequate in the dominant lethal assay.

Other mutagenic mechanisms

6) In vitro sister chromatid exchange (SCE) in Chinese hamster ovary cell assay (MRID No. not available; Doc. No. 005095/005588): The test is positive in the presence of S9 activation; dose related increases in SCEs were obtained at 50-200 µg/mL. Without S9 activation the test is negative up to cytotoxic levels (≥40 µg/mL).

7) Unscheduled DNA synthesis in cultured human fibroblasts (WI-38) assay (MRID No.

00124901; Doc. No. 005095/005588): The test is negative up to a precipitating dose (10^{-3} M +/- S9).

Conclusions

In vitro, methyl parathion was negative for gene mutations in S. typhimurium, E. coli and S. cerevisiae. It also did not cause mitotic recombination or gene conversion in S. cerevisiae or DNA damage in a human cell line. Gene mutations and SCE were, however, induced in cultured mammalian cells and the effect was more clearly demonstrated in the presence of S9 activation. The only acceptable in vivo study in the Agency's files indicated that methyl parathion was not active in the mouse dominant lethal assay. Nevertheless, positive dose-related increases in micronuclei induction have been reported in the literature in mice receiving methyl parathion orally (Mathew et al., 1990) and in rats following intraperitoneal injection (Grover and Malhi, 1985). Structural chromosome aberrations have also been reported in bone marrow cells harvested from treated rats (Malhi and Grover 1987).

The relevance of the positive findings from both the in vitro and in vivo mutagenicity studies is not clear in light of the negative cancer studies and the lack of an effect in germinal cells in the dominant lethal assay. The Committee concluded, therefore, that nothing further would be gained by requiring additional testing. Based on these deliberations, the available acceptable studies satisfies the Pre-1991 mutagenicity initial testing battery guidelines. No further testing is required at this time.

g. Metabolism

In a metabolism study in rats (MRID No. 41001407), Methyl parathion (U-^{14}C-phenyl-labeled) was administered orally to male and female rats in order to follow the absorption, distribution, excretion and metabolism of the radio-labeled molecule after single oral administration of the test material at 2 dose levels and after repeated oral (14x) pre-treatment using the non-radioactive test material followed by single oral administration of the ^{14}C-labeled material.

The data showed that a large proportion of the administered radioactivity was absorbed from the gastro-intestinal tract and excreted in the urine. Within 8 hours, 61.8 to 94% of the radioactivity was excreted in the urine of male and female rats. After 48 hours the corresponding values were 75.7 to 99.2% and, at this interval, 3.2 to 9.3 of the administered radioactivity was excreted in feces. Only negligible amounts of administered radioactivity was found in organs, tissues, blood (<0.1-1.0%) and expired air (<0.01%). Total average recoveries for both sexes ranged from 95.6 to 104.2%.

Repeated oral (14x) administration of non-labeled methyl parathion had no apparent effect on the rate of absorption and excretion of the ^{14}C-labeled material or on the levels of residual radioactivity in organs/tissues and blood.

Similar metabolic patterns were found in urine and feces regardless of the dose of test material administered.

Seven metabolites were detected in urine, 5 of which were characterized. The characterized metabolites represented up to 94.7% of the radioactivity recovered in urine. The two major urinary metabolites were the sulphate conjugate of para-nitrophenol (60.6 to 79.3% of urinary radioactivity) and the glucuronide conjugate of para-nitro-phenol (up to 15% of urinary radioactivity). Three minor metabolites detected were para-nitrophenol, P-O-desmethyl-paraoxon-methyl and P-O-desmethyl-parathion-methyl; small amounts of the latter 2 metabolites ere also found in feces. Although only 2 of the 6 metabolites detected in fecal extracts were characterized, the total radioactivity recovered in feces was quite low (1.0 to 4.2% of administered dose). The parent compound was not detected in either urine or feces.

Core classification: minimum.

h. Neurotoxicity

Available neurotoxicity studies were adequate to satisfy the guideline requirements, however the Committee determined the need for a developmental neurotoxicity study (see below).

Acute neurotoxicity in hens

In an acute delayed neurotoxicity study in hens (MRID No. 41606801), Methyl parathion (purity 95.8%) was administered to hens (10/group, followed by an additional 6 in the methyl parathion group, because of high mortality in the initial dose group) via oral intubation, one acute dose of 0 or 250 mg/kg, redosed at 0 or 215 mg/kg on day 21 (intra-muscular atropine sulfate was administered concurrently, as needed). TOCP at 600 mg/kg was the positive control.

A total of 6 (out of 16) hens died following the first dose of methyl parathion; 2 additional deaths followed the second dose. Cholinergic signs (including lethargy, loss of coordination, salivation, shallow and rapid respiration) were seen for up to 8 days following the first dose and 6 days following the second dose. One hen displayed left leg stiffness after the second dose until study termination; other birds were normal after acute signs had resolved. No signs of ataxia typical of delayed neurotoxic effects were seen in control or methyl parathion-treated birds after either dose, nor were neural degenerative changes were observed histologically. TOCP-treated birds displayed behavior and histopathological changes typical of delayed peripheral neuropathy.

Based on the results of this study the NOEL for acute delayed neurotoxicity in laying hen was established at 215 mg/kg. A NOEL for systemic toxicity was not established.

The initial study report did not include verification of concentration of dosing solutions, and so the study was initially rated supplementary. After dose verification data was received, the study was upgraded to Core-minimum [Guideline 81-7].

In their memo of July 7, 1998, the Committee requested submission of a confirmatory NTE study for methyl parathion, since NTE inhibition was not measured in the above study. During the comment period, registrant submitted a literature reference (Ohkawa, H., H. Oshita, and J. Miyamoto, 1980) that included an evaluation of NTE inhibition by methyl parathion. Hens were

evaluated for acetylcholinesterase and NTE inhibition (in the brain) 2 days after oral dosing with 100 mg/kg methyl parathion. Acetylcholinesterase was found to be 85% inhibited, while NTE inhibition was only 12%. The submitted data, taken together with the negative hen study, are sufficient to demonstrate that methyl parathion does not cause acute delayed neuropathy. A confirmatory NTE study will not be required.

Acute neurotoxicity in rats

In an acute neurotoxicity study (MRID No.: 43254401), male and female Sprague-Dawley rats (10 animals/sex/group) were orally gavaged once with methyl parathion at doses of 0, 0.025, 7.5, 10 (males only), or 15 (females only) mg/kg.

Neurobehavioral evaluation revealed treatment-related FOB and motor activity findings at the mid- and high-dose levels (lacrimation, salivation, miosis, tremors/convulsions, muscle fasciculations, muscle weakness, and ataxia).

Neuropathological findings consisted of focal demyelination in the dorsal root fibers of the cervical spine in 3/6 high-dose males and lumbar spine in 3/6 low-, 4/6 mid- and 5/6 high-dose males. Focal demyelination was also observed in the ventral root fibers of the cervical spine in 2/6 high-dose males and of the lumbar spine in control (males, 2/6; females, 1/6), low- (males, 3/6), mid- (males, 4/6), and high- (males, 4/6; females, 3/6) dose groups. Focal demyelination of the lumbar spinal cord and spinal nerve were observed in high-dose males; the incidence of each of these observations was only 1/6. Focal demyelination was observed in the tibial nerves of 1/6 mid- and 3/6 high-dose males and in the sural nerves of 2/6 high-dose males.

In summary, systemic toxicity was observed in high-dose males (decreased body weight gain) and females (increased incidence of clinical signs). Neurotoxic effects (abnormal FOB findings, decreased motor activity, inhibition ChEase activities, and neuro-pathological findings) were observed in mid- and high-dose males and females.

Based on the results of this study, the systemic LOEL was 10 mg/kg (males) and 15 mg/kg (females); the systemic NOEL was 7.5 mg/kg. In males and females, the LOEL for neurotoxicity was 7.5 mg/kg; the NOEL for neurotoxicity was 0.025 mg/kg.

This study is classified as Core-Guideline and satisfies guideline requirements (81-8) for an acute neurotoxicity screening battery in the rat.

Subchronic neurotoxicity in rats

In a subchronic neurotoxicity screening battery (MRID No. 43490501), methyl parathion was administered to groups of Crl:CD BR (Sprague-Dawley) male and female rats for 13 weeks at dietary concentrations of 9 (basal diet), 0.5, 5 or 50 ppm (equivalent to 0, 0.029, 0.295, or 3.02 mg/kg/day, males; 0, 0.037, 0.365, or 3.96 mg/kg/day, females).

No treatment-related differences were noted in motor activity or the incidence of gross and neuropathological lesions at any dose level. No treatment-related effects were observed at 0.5 ppm.

At 5 ppm, inhibition in RBC ChE activities in males (-19 to -33%) at weeks 4, 8, and 14 and in females (-23 to -24%) were observed at weeks 8 and 14.

At 50 ppm, females showed significant decreases in mean body weights (-6.6 to -11.4%) during weeks 2 to 6 and a significant decrease (-13.5%) in mean body weight gain for weeks 1 to 13. FOB findings consisted of tremors in females at weeks 4 and 8, partial (absent) pupillary response in males and females during the week 4 evaluation, slow pupillary constriction in males and females during weeks 8 and 13, and significant decreases in hindlimb grip strength in females at weeks 4 and 13. Plasma (-61 to -66%, males; -80 to -35%, females), RBC (-52 to -66%, males; -55 to -64%, females) and regional brain (-38 to -75%, males; -66 to -93%, females) ChE activities were all inhibited. During the treatment-free recovery period, plasma ChE showed complete recovery in males and females. RBC ChE and regional brain (excluding cerebral cortex and cerebellum in males, which showed nearly complete recovery) ChE activities in males and females showed partial recovery but were still significantly lower than concurrent control values.

Based on the results of this study (inhibition of RBC ChE), the LOEL was established at 5 ppm (0.295 mg/kg/day, males, 0.365 mg/kg/day, females); the NOEL was established at 0.5 ppm (0.029 mg/kg/day, males; 0.037 mg/kg/day, females).

This study is classified as Acceptable and satisfies guideline requirements (section 82-7) for a subchronic neurotoxicity screening battery in the rat.

Chronic neurotoxicity in rats

In a twelve month oral neurotoxicity study in rat (MRID No. 41853801, 44204501), Methyl parathion (purity 94.6%) was administered to Sprague Dawley rats (70/sex/group; 50 primarily for neuropathology, 20 primarily for ocular effects) in feed at 0, 0.5, 2.5, 12.5, and 50 ppm (daily intake was 0, 0.02, 0.107, 0.533, and 2.207 mg/kg/day for males, 0, 0.026, 0.138, 0.697, and 3.088 mg/kg/day for females).

No ocular effects were seen at any dose level.

Compound-associated clinical signs (e.g. aggressiveness, tremors, abnormal gait, decreased body weight and body weight gain, increased food consumption, etc.) were seen at 50 ppm dose only. Plasma, erythrocyte, and brain cholinesterase activity were significantly decreased in males and females at 12.5 ppm and 50 ppm doses (at various time points). For erythrocyte cholinesterase, inhibition ranged from 3-13% at 12.5 ppm, 13-20% at 50 ppm; for plasma cholinesterase, inhibition ranged from 25-36% at 12.5 ppm, 52-79% at 50 ppm; for brain cholinesterase, inhibition ranged from 4-25% at 12.5 ppm, 57-75% at 50 ppm. Increased neuropathology in the spinal cord (lumbosacral spine, neuronal degeneration) was seen in males and females at 50 ppm dose only. Increased neuropathology in peripheral nerve preparations was seen in both sexes at all doses, however the dose at which the changes are compound-associated or toxicologically relevant was determined to be 12.5 ppm, with a NOEL of 2.5 ppm.

Based on the results of this study, the NOEL for ocular effects was > 50 ppm (2.2 mg/kg/day), the LOEL for systemic effects (decreased body weight, increased food consumption, and clinical signs) was 50 ppm (2.2 mg/kg/day), NOEL was 12.5 ppm (0.53 mg/kg/day). The LOEL for cholinesterase inhibition was 12.5 ppm (0.53 mg/kg/day), with a NOEL of 2.5 ppm (0.11 mg/kg/day); the LOEL for neuropathological effects was 12.5 ppm (0.53 mg/kg/day), with a NOEL of 2.5 ppm (0.11 mg/kg/day).

This study is classified as acceptable and is not a guideline study.

I. Dermal absorption

No study was available. Based on available information, including comparison of toxicity following oral and dermal exposure, dermal absorption was estimated to be 100% (i.e. equivalent toxicity is expected after oral or dermal exposure to a given amount of methyl parathion). This decision was reevaluated and reaffirmed in the HIARC meeting of March 4, 1999 (see HIARC memo of 3/23/99).

j. Reference Dose (RfD) for Chronic Oral Exposure

The Chronic RfD for methyl parathion was established at 0.0002 mg/kg/day, based on systemic toxicity, neuropathology, and RBC cholinesterase inhibition occurring at a LOEL of 0.21 mg/kg/day in the two year chronic rat study (MRID No. 252501-252503). The NOEL of 0.02 mg/kg/day will be used for risk assessment. An uncertainty factor of 100 was applied to account for both interspecies extrapolation and intraspecies variability. An additional Safety Factor of 10, required for the protection of infants and children in accordance with the FQPA, will be retained in addition to the traditional Uncertainty Factor (see discussion below). The Population Adjusted Dose (PAD) was established at 0.00002 mg/kg/day.

Based on the toxicology data available, including two carcinogenicity studies in rats (MRID No. 252501-252503, Accession Nos. 257513, 257514), and one in mice (MRID No. 42216401), the Hazard Identification Committee determined that methyl parathion did not alter the spontaneous tumor profile in rats and mice under the testing conditions. Therefore, it was recommended that methyl parathion be classified as a **"Group E"**, indicating evidence of non-carcinogenicity for

humans; i.e., the chemical is characterized as **"Not Likely"** to be carcinogenic in humans via relevant routes of exposure.

k. Uncertainty Factor/FQPA Considerations

The following evaluation of the chemical methyl parathion is provided to address FQPA considerations on the sensitivity of infants and children.

Summary of reproductive and developmental toxicity (see also above):

A two-generation reproduction study was conducted with Sprague-Dawley rats (15 males and 30 females/group) (MRID 00119087; Doc. 005095, 005588) in which methyl parathion (93.65%) was administered in the diet at levels of 0.5, 5, or 25 ppm (0.04, 0.38, or 2.0 mg/kg/day for males and 0.04, 0.44, or 2.3 mg/kg/day for females). The parental (systemic) NOEL was 5 ppm (0.44 mg/kg/day), and the parental LOEL was 25 ppm (2.3 mg/kg/day), based on decreased premating body weight for F1 females and decreased maternal body weight during lactation in females of both generations. No parental reproductive toxicity was observed at any dose level; however, the offspring/developmental NOEL was 5 ppm (0.44 mg/kg/day), based upon decreased pup survival in early lactation and on decreased body weight gain and increased food consumption in the period immediately following weaning. The developmental LOEL was 25 ppm (2.3 mg/kg/day). It was noted that cholinesterase activity was not measured in either adults or offspring in this study. (Daly and Hogan, 1982)

In a prenatal developmental toxicity study in Wistar rats (MRID 41136101; Doc. 008118, 009526), doses of 0.3, 1.0, or 3.0 mg/kg/day methyl parathion (97%) were administered by gavage in a dose volume of 10 ml/kg of 0.5% aqueous Cremophor on gestation days 6-15. Each group consisted of 25 rats; 10 additional rats each were assigned to the control and high-dose groups for maternal cholinesterase measurements. Cesarean section was performed on gestation day 21. The maternal NOEL was 1.0 mg/kg/day, with a maternal LOEL of 3.0 mg/kg/day, based upon increased mortality; adverse clinical signs (somnolence, ataxia, dyspnea, ventral recumbency, and repeated chewing behavior); decreased body weight, body weight gain, and food consumption; and decreased plasma, erythrocyte, and brain cholinesterase activity. The developmental NOEL was also 1.0 mg/kg/day; the developmental LOEL (3.0 mg/kg/day) was based on increased postimplantation loss (early resorptions), decreased fetal body weight, and increased incidence of delayed ossification (3rd cervical vertebra, proximal phalanx of the 2nd right digit, and 1st metatarsal of both hindlimbs). (Becker et al., 1987)

In a prenatal developmental toxicity study conducted in Himalayan rabbits (15/group) (MRID 259403, 259404, 259405; Doc. 004997, 007614), methyl parathion (95.7%) was administered by gavage in 0.5% aqueous Cremophor at dose levels of 0.3, 1.0, or 3.0 mg/kg/day on days 6-18 of gestation. These dose levels were based upon a previously conducted study with rabbits (MRID 41046101) in which plasma and erythrocyte cholinesterase inhibition was observed at a dose of 3.0 mg/kg/day, and for that reason they were considered adequate, although cholinesterase activity was not measured in this study. No evidence of either maternal or developmental toxicity was observed (NOEL $\geq$3.0 mg/kg/day). (Renhof, 1984)

Additional information submitted by Cheminova during the comment period:

In their response to HED's preliminary risk assessment, Cheminova submitted additional information regarding several toxicity studies relevant to FQPA considerations. HED's assessment of that additional information is summarized below:

An additional guideline developmental study in rabbits was submitted during the comment period (MRID 44691004). Methyl parathion (purity 95.7%) was administered by gavage at doses of 0, 0.3, 3, or 9 mg/kg to artificially inseminated rabbits on gestation days 6-18. Preliminary review indicates that no developmental effects were seen at any dose. In does, RBC cholinesterase inhibition was seen at all doses, and plasma cholinesterase inhibition was seen at 9 mg/kg (measured in does at 2 h post-dosing on gestation day 18). Cholinesterase inhibition was not measured in pups.

An additional non-guideline multi-generation reproduction study in rats was also submitted during the comment period (MRID 44768201). Methyl parathion (purity 95%) was administered to Wistar rats in the diet at 2, 10, or 50 ppm. Administration was continued through three generations, two matings per generation. There was a large decrease in pup survival at 50 ppm, such that no third generation matings could be conducted at that dose. There was a slight, sporadically statistically significant, decrease in pup survival at 10 ppm. No effects were seen at 2 ppm. In addition, although no effects on fertility or gestation were seen, surviving F_{1b} animals receiving 50 ppm suffered occasional convulsions (not noted in F_0 parents at this dose). No F_{2b} pups survived to adult at 50 ppm. Doses used in this study were intermediate to those used in the submitted Guideline reproduction study (see above), and results seen in this study do not conflict with those noted previously. However, the effects seen at 50 ppm in the current study (decreased survival and convulsions) support the request for a developmental neurotoxicity study (see below).

An additional developmental study in rats (MRID 00143747) was also cited by Cheminova in their comments. This study has been previously reviewed (HED Doc. No. 005095) and found to be supplementary due to reporting deficiencies. Based on the previous HED review, it was found that maternal toxicity was not established, but that methyl parathion was "embryotoxic or fetotoxic at 1.0 mg/kg, but not at 0.3 mg/kg." Based on the many deficiencies cited in the HED review, we do not consider the study

suitable for use in risk assessment, however we note that the results of the earlier review do not support Cheminova's contention that "fetal toxicity (decreased body weight) was evident only in the presence of maternal toxicity."

Additional information from the literature: (Although these studies were not submitted to the Agency by the Registrant in support of registration or reregistration, they can be considered in weight-of-the-evidence determinations for methyl parathion.)

Effects on gestation and morphological development following *in utero* exposure:

Fuchs, V., S. Golbs, M. Kuehnert, and F. Osswald. (1976) Untersuchungen zur praenatal-toxischen wirkung von parathion-methyl an Wistarratten im vergleich zu cyclophosphamid und trypanblau. *Archives of Experimental Veterinary Medicine (Leipzig)* 30(Mai3):343-350.

Methyl parathion (0.1, 1.0, or 3 mg/kg) was administered orally to Wistar rats on gestation days (5-9 and 11-15) or (5-9 and 11-19 [3.0 mg/kg dose only]), at intervals of 2 days. Growth retardation and increased incidence of resorptions were noted in the 3.0 mg/kg dose group, although malformations were not observed. Maternal toxicity (decreased body weight and clinical signs) was also seen at the 3.0 mg/kg dose.

Sunil Kumar, K.B. and K.S. Devi. (1996) Methyl parathion induced teratological study in rats. *Journal of Environmental Biology* 17(1):51-57.

Pregnant inbred Wistar rats (10/group) were administered methyl parathion (98% a.i.) on gestation days 6 through 15 at gavage doses of 0.5, 1, and 1.5 mg/kg/day. The dams were killed on gestation day 20 and fetuses were examined for external and visceral anomalies. At 1.5 mg/kg/day, there was a significant decrease in maternal body weight gain during gestation and clinical signs indicative of cholinesterase inhibition were seen in some dams; at the same dose, an increase in resorptions and a decrease in fetal and placental weight were observed. There was no increase in skeletal or viscera abnormalities; however, a significant increase in the incidence of "hemorrhagic spots" in the brain (ventricles) and upper body were observed in pups from dams treated with 1.5 mg/kg/day methyl parathion.

Assessment of postnatal functional toxicity following prenatal exposure:

Gupta, R.C., R.H. Rech, K.L. Lovell, F. Welsch, and J.E. Thornburg. (1985) Brain Cholinergic, behavioral, and morphological development in rats exposed *in utero* to methyl parathion. *Toxicology and Applied Pharmacology* 77:405-413.

In this study, male Fischer 344 rats were mated to Wistar-Furth females. The dams were administered 0 or 1.0 mg/kg/day of methyl parathion in peanut butter (0.1 g/25 g body weight) as a dietary dose consumed in <2 minutes, or 0 or 1.5 mg/kg/day of methyl parathion by gavage in peanut oil (at a volume of 0.1 ml/50g body weight). Treatment

was administered daily from gestation day 6 through 20. The dams were allowed to litter normally, and pups were placed with foster mothers within 24 hours of birth.

At specified intervals (gestation day 19 for dams, postnatal days 1, 7, 14, 21, and 28 for pups), brains were removed, weighed, dissected, and processed for analysis of acetylcholinesterase (AChE) and choline acetyltransferase (CAT) activity and of [^{3}H]quinuclididinyl benzilate (^{3}H-QNB) binding to muscarinic receptors. For pups, frontal cortex and brainstem were collected on postnatal days 1 and 7, while striatum and hippocampus were also obtained on postnatal days 14, 21, and 28. Tissues from two pups per litter were pooled, and the litter was used as the unit of analysis. In addition, morphological analysis (cell counts) of the cornuammonis in the hippocampus (pyramidal cells) and of the cerebellar culmen (granule cells) was performed in 4 control and 4 high-dose pups at 28 days of age.

Behavioral evaluation of the pups was performed as follows: preweaning reflexive behaviors (postnatal days 1-25); startle response (days 1-25 and 4 months); passive avoidance, rotarod performance, and accommodated locomotor activity (2 months); cage emergence (3 months); shuttle box avoidance (4 months); and operant behavior (3-6 months).

The following treatment-related effects were noted in dams: at 1.5 mg/kg/day, clinical signs of toxicity in dams included muscle fasciculations and tremors, decreased maternal body weight gain and increased late resorptions; no clinical signs were seen at 1.0 mg/kg/day. At gestation day 19 (the only time point measured), there was a dose-dependent decrease in AChE activity, an increase in cortical CAT activity, and a reduction in ^{3}H-QNB binding sites (B_{max}) with no alteration of $K_{D.}$

On postnatal day 1, litter size, body weight, and pup brain weight were similar between control and treated groups. Prenatal exposure to 1.5 mg/kg/day reduced AChE and increased CAT activity in all brain regions at all developmental periods (post-natal days 1, 7, 14, 21, and 28). Similar exposure to 1.0 mg/kg/day caused a significant but smaller and less persistent reduction in AChE activity (statistically significant in the frontal cortex only on post-natal day 1, in brainstem on post-natal days 1-21, but not day 28) but no change in brain CAT activity of the offspring. Neither dose level altered the ^{3}H-QNB binding in frontal cortex or striatum on post-natal day 28 (the only time point for which results were reported). Cage emergence, accommodated locomotor activity, and operant behavior in a mixed paradigm were impaired in rats exposed to 1.0 but not to 1.5 mg/kg/day. The reason for the apparent lack of a dose-response relationship for the behavioral parameters was not clear.

Comparison of the neurotoxic response of adults and neonatal or weanling animals:

Benke, G.M. and S.D. Murphy. (1975) The influence of age on the toxicity and metabolism of methyl parathion in male and female rats. *Toxicology and Applied Pharmacology* 31:254-269.

The effects of methyl parathion and methyl paraoxon were studied in male and female Holtzman rats ranging in age as follows: 1, 12-13, 23-24, 35-40, and 56-63 days of age. The test substances were administered by i.p. injection in corn oil at a volume of 1 ml/kg over a range of doses. It was found that there was a gradual decrease in susceptibility to methyl parathion with increasing age for both sexes as measured by the value of the LD50. For methyl parathion, the LD50 ranges from 1 mg/kg at postnatal day 1 to 6-8 mg/kg on postnatal day 56-63. Age differences in susceptibility were not related to differences in sensitivity of cholinesterase to inhibition by methyl paraoxon *in vitro*. LD50 values were calculated for the different ages; in general, changes in LD50 values with age for methyl parathion correlated better with changes in rates of reactions which represented detoxification pathways for methyl paraoxon than for reactions which represented direct metabolism of the parent compound. Both male and female rats became less sensitive to the acute lethal effects of methyl paraoxon with increasing age. This is consistent with a hypothesis that changes in LD50 values of methyl parathion with age are due to changes in rates of metabolism of the oxygen analogs.

Pope, C.N., T.K. Chakraborti, M.L. Chapman, J.D. Farrar, and D. Arthun. (1991) Comparison of in vivo cholinesterase inhibition in neonatal and adult rats by three organophosphorothioate insecticides. *Toxicology* 68:51-61.

The time course of cholinesterase inhibition and recovery in whole brain was compared between neonatal (postnatal day 7) and adult (80-100 days of age) Sprague-Dawley rats after acute treatment (by subcutaneous injection) with maximum tolerated doses of methyl parathion and other organophosphate pesticides (chlorpyrifos and parathion). The neonates were more sensitive clinically than adults to chlorpyrifos exposure: the MTD for neonates was 7.8 mg/kg s.c., while for adults the MTD was 18 mg/kg s.c. In general, maximal brain ChE inhibition was similar (>78%) in both age groups, but ChE activity recovered faster in neonates. Plasma and RBC ChE activities correlated relatively well with brain ChE activity in neonatal rats at all time points between 4 hours and 7 days posttreatment, but similar correlations between circulating and brain ChE activities in adults were more variable. The study authors concluded that neonatal rats are more sensitive to acute lethality from methyl parathion (and other OP) exposure than are adults, and that MTD exposures produced extensive brain ChE inhibition in both age groups. Following OP exposures, however, significant compound-related and age-related differences in the duration of ChE inhibition can occur.

Pope, C.N. and T.K. Chakraborti. (1992) Dose-related inhibition of brain and plasma cholinesterase in neonatal and adult rats following sublethal organophosphate exposures. *Toxicology* 73:35-43.

Dose-related inhibition of both brain and plasma cholinesterase activity was examined in neonatal and adult rats exposed to methyl parathion and other organophosphate pesticides (chlorpyrifos and parathion) by subcutaneous injection in corn oil at 1-2 ml/kg. It was found that ED_{50} estimates for both brain and plasma cholinesterase correlated highly with previously derived MTD values. The correlation between the extent of brain and plasma

cholinesterase inhibition across dose in neonatal rats was high but lower in adults. The study authors concluded that in vivo inhibitory potency, towards either brain or plasma ChE activity, of methyl parathion and the other organophosphate pesticides tested, is highly correlated with sensitivity to acute toxicity in both neonatal and adult rats.

Additional information submitted by World Wildlife Fund during the comment period:

In their comments, World Wildlife Fund (WWF) has submitted a large number of articles in support of their contention that there is evidence indicating that methyl parathion may function as an endocrine disrupter. Two of the articles (Lukaszewica-Hussain, Moniuszko-Jakoniuk, and Pawlowska; and Dhondup and Kaliwal) concerned possible effects in mammals (rats). This issue is discussed more fully in the EFED Chapter.

Recommendation for a developmental neurotoxicity study: The Committee determined that a developmental neurotoxicity study should be required for methyl parathion. It was further recommended that the protocol should include comparative measurements of cholinesterase inhibition in adults and offspring. The weight-of-evidence used in arriving at this conclusion is presented below:

Evidence that support requiring a developmental neurotoxicity study:

Methyl parathion is a neurotoxic chemical.

- SAR: Methyl parathion is an organophosphate chemical.
- Administration to various species (rat, mouse, dog, rabbit) results in ChE inhibition in the plasma, RBCs, and brain.
- Neurobehavioral effects (e.g., lacrimation, salivation, miosis, tremors, convulsions, muscle fasciculation, muscle weakness, ataxia) were observed in rats in an acute neurotoxicity study at a gavage dose of 7.5 mg/kg. In the subchronic neurotoxicity study, tremors, slow pupillary constriction, and decreased hindlimb grip strength were observed at 50 ppm (3.02/3.96 mg/kg/day in M/F).
- Neuropathological findings observed in the acute neurotoxicity study in rats (at doses of 7.5 mg/kg or higher) included focal demyelination of the dorsal and ventral root fibers of the cervical and lumbar spinal cord and focal demyelination of the sural and tibial nerves. In a one-year neurotoxicity study in rats, neuropathological findings were observed in peripheral nerves and/or spinal cord at doses of 12.5 ppm or higher (0.5 mg/kg/day or higher). In the two-year chronic study in Sprague-Dawley rats, loss of myelinated sciatic nerve fibers and retinal atrophy were observed at 50 ppm (2.5 mg/kg/day); increased severity of sciatic nerve degeneration (in males only) was also seen at 5 ppm (0.3 mg/kg/day).

There is evidence of the developmental neurotoxic potential of Methyl parathion in the open literature. In a study by Gupta, et al. (1985), it was demonstrated that both maternal and fetal neurobiochemical markers are affected by treatment with 1.0 or 1.5 mg/kg/day from gestation days 6-20. Behavioral alterations were detected at 1.0 mg/kg/day only. Although the behavioral alterations detected are difficult to interpret, due to the lack of a

dose-response relationship, the changes in neurochemical parameters were dose-related and persistent. In particular, decreases in acetylcholinesterase and increases in choline acetyltransferase seen at 1.5 mg/kg/day (exposure to dams only, during gestation days 6-20) persisted throughout the study period, and remained statistically significantly different from control values 28 days after cessation of exposure.

In studies by Benke and Murphy (1975), Pope et al. (1991), and Pope and Chakraborti (1992), increased sensitivity of young rats to acute effects of methyl parathion, as compared to adults, was observed.

In submitted reproduction studies (MRID 00119087, MRID 44768201) decreased survival of pups was seen at doses causing less severe effects in adults. At 50 ppm (MRID 44768201), convulsions were noted in surviving F_{1b} offspring; no such effects were noted in F_o adults.

Submitted articles from the open literature (see above) raise the possibility that methyl parathion may disrupt endocrine function.

Evidence that do not support asking for a developmental neurotoxicity study:

Brain weight was increased in the three-month study in mice at 60 ppm (13.5/16.2 mg/kg/day in M/F) and in the two-year chronic study in rats at 50 ppm (2.5 mg/kg/day). These effects were, however, not statistically significant and were not considered to be biologically meaningful. In a study from the open literature (Gupta et al., 1985) it was reported that pup brain weights (Day 1) were not affected following *in utero* exposure to Methyl parathion (gestation days 6-20).

Delayed neuropathy was not observed in the hen.

No evidence of abnormalities in the development of the fetal nervous system was observed in the prenatal developmental toxicity studies in either rats, or rabbits, at maternal gavage doses up to 3.0 mg/kg/day. In the two-generation reproduction study in rats (MRID 00119087), no clinical evidence suggestive of neurotoxicity was observed grossly in pups, which had been administered Methyl parathion *in utero* and during early and late postnatal development, generally mediated by maternal dietary exposure, but also available in the diet to late lactation pups.

FQPA assessment of additional sensitivity for infants and children:

Under the Food Quality Protection Act (FQPA), P.L. 104-170, which was promulgated in 1996 as an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA), the Agency was directed to "ensure that there is a reasonable certainty that no harm will result to infants and children" from aggregate exposure to a pesticide chemical residue. The law further states that in the case of threshold effects, for purposes of providing this reasonable certainty of no harm, "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide residue only if, on the basis of reliable data, such margin will be safe for infants and children."

Pursuant to the language and intent of the FQPA directive regarding infants and children, the applicable toxicity database for Methyl parathion was evaluated by the Hazard Identification SARC.

Adequacy of data package: The data package included an acceptable two-generation reproduction study in rats and acceptable prenatal developmental toxicity studies in rats

and rabbits, meeting the basic data requirements, as defined for a food-use chemical by 40 CFR Part 158. The Committee determined that a developmental neurotoxicity study should be required for methyl parathion.

Susceptibility issues: The submitted guideline study data provided no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to Methyl parathion. In the prenatal developmental toxicity study in rats, developmental toxicity was observed only in the presence of maternal toxicity; the maternal and developmental NOELs and LOELs were equivalent at 1.0 and 3.0 mg/kg/day, respectively. In the prenatal developmental toxicity study in rabbits, neither maternal nor developmental toxicity was observed, although, based upon the results of a previous study in rabbits, the doses were judged to be adequate to elicit plasma and erythrocyte cholinesterase inhibition in the maternal animals. In the two-generation reproduction study in rats, offspring toxicity occurred at the same dose as parental toxicity; the offspring developmental and parental systemic NOELs and LOELs were 5 ppm (0.25 mg/kg/day) and 25 ppm (1.25 mg/kg/day), respectively.

An assessment of the differential response of fetuses versus adults to cholinesterase inhibition following oral administration of Methyl parathion was studied by Gupta, et al. (1985). No indication of additional sensitivity of the offspring was suggested by the data, since offspring effects were noted concurrently with maternal effects. Specifically, it was demonstrated that both maternal and fetal neurobiochemical markers are affected by treatment with 1.0 or 1.5 mg/kg/day from gestation days 6-20, and that neurochemical markers in exposed pups remained significantly different from those of control pups for as long as 28 days after cessation of exposure.

In addition, in studies by Benke and Murphy (1975), Pope et al. (1991), and Pope and Chakraborti (1992), evidence of increased sensitivity of young rats to the effects of methyl parathion, as compared to adults, was reported. Although these studies used non-oral methods of test substance administration, and were conducted at the maximum tolerated dose in order to establish LD50 values, they indicate that there should be a concern for the effects of methyl parathion on young animals. This concern is reinforced by the marginal decrease in survival seen in an additional reproduction study at a dose of 10 ppm; no effects were seen in adults at that dose (MRID 44768201).

Uncertainty factor: The Committee determined that for methyl parathion the 10-fold uncertainty factor for the protection of infants and children is appropriate, based upon the following concerns:

1. The data base for methyl parathion is complete with regard to the standard studies required by 40 CFR Part 158 for a food-use chemical. Acceptable prenatal developmental toxicity studies in rats and rabbits, and an acceptable multigeneration reproduction study in rats have been received by the Agency. Delayed neuropathy was not observed in a study in hens. A single-dose acute neurotoxicity study in rats demonstrated neuropathology in males at 7.5 mg/kg; more severe effects were seen in males at 10 mg/kg and in females at 15 mg/kg.

Neuropathology was also seen in the one year neurotoxicity study in rats at doses of 0.53 mg/kg/day and above, and increased severity of neuropathological lesions was seen in a two-year chronic toxicity study in rats at doses of 0.2 mg/kg/day and above. There was evidence of the developmental neurotoxic potential of Methyl parathion in the open literature (Gupta et al., 1985); in this study, alterations in neurochemical markers of pups persisted for at least 28 days following *in utero* exposure. A developmental neurotoxicity study is required with methyl parathion; in the absence of this study, substantial uncertainties remain regarding the effect of methyl parathion on functional development.

2. Although differential sensitivity to young animals was not revealed in standard prenatal developmental and multigeneration reproductive toxicity studies, qualitative evidence of increased sensitivity to perinatal rats has been identified in the open literature. In these studies, a) lethality at doses at or near the maximum tolerated dose and b) cholinesterase inhibition were used as biomarkers of sensitivity. Methyl parathion was administered to the rats in these studies by subcutaneous injection (Pope et al., 1991; Pope and Chakraborti, 1992), intraperitoneal injection (Benke and Murphy, 1975), or oral (Gupta, 1985) routes. This evidence of increased sensitivity to the offspring cannot be quantified.

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l. Toxicity End-Point Selection

1. DERMAL ABSORPTION FACTOR

No study was available. Based on available information, including comparison of toxicity following oral and dermal exposure, dermal absorption was estimated to be 100% (i.e. equivalent toxicity is expected after oral or dermal exposure to a given amount of methyl parathion). This decision was reevaluated and reaffirmed in the HIARC meeting of March 4, 1999 (see HIARC memo of 3/23/99).

2. REFERENCE DOSE FOR ACUTE EXPOSURE (ONE DAY)

For acute dietary exposure, the one year rat neurotoxicity study (MRID No.: 41853801, 44204501) was selected, based on neuropathology and cholinesterase inhibition occurring at a LOEL of 0.53 mg/kg/day. The NOEL of 0.11 mg/kg/day will be used for risk assessment. An UF of 100 will be used, resulting in an acute dietary RfD of 0.0011 mg/kg/day. An additional Safety Factor of 10, required for the protection of infants and children in accordance with the FQPA, will be retained in addition to the traditional Uncertainty Factor. The Population Adjusted Dose (PAD) was established at 0.00011 mg/kg/day.

Previously, the HIARC had selected the acute oral neurotoxicity study for use in acute dietary risk assessment (HIARC Report, 12/1/97). Effects seen at 7.5 mg/kg (the mid-dose) in this study included cholinesterase inhibition, changes in functional observation battery and motor activity, and neuropathology. Therefore, the NOAEL from this study was set at 0.025 mg/kg (the low dose). Because the mid and low doses used in this study differed by a factor of 300, the registrant requested reconsideration of this endpoint, and suggested several possible alternatives.

On March 4, 1999, the Committee evaluated available data for methyl parathion, and concluded the only appropriate study demonstrating a higher NOAEL for the endpoints measured in the acute neurotoxicity study was the special one year chronic neurotoxicity study. The study included a dose intermediate between the LOAEL and NOAEL of the guideline subchronic neurotoxicity study (0.295 and 0.029 mg/kg/day, respectively, based on red blood cell cholinesterase inhibition), and critical endpoints identified in the acute oral neurotoxicity study (cholinesterase inhibition and neuropathology) were evaluated. The Committee felt that use of this study for acute dietary risk assessment would not underestimate the risk for that type of

exposure, due to the longer duration of the selected study (one year vs. a single exposure) and the evaluation of the critical effects (cholinesterase inhibition and neuropathology). The Committee felt that use of a NOEL from a long term (one year) study would be protective for a single exposure.

3. SHORT TERM OCCUPATION EXPOSURE (1 TO 7 DAYS)

For short term occupational or residential exposure, the one year rat neurotoxicity study (MRID No.: 41853801, 44204501) was selected, based on neuropathology and cholinesterase inhibition occurring at a LOEL of 0.53 mg/kg/day. The NOEL of 0.11 mg/kg/day will be used for risk assessment. An UF of 100 will be used.

4. INTERMEDIATE TERM OCCUPATIONAL EXPOSURE (1 WEEK TO SEVERAL MONTHS)

For intermediate term occupational exposure, the one year rat neurotoxicity study (MRID No.: 41853801, 44204501) was selected, based on neuropathology and cholinesterase inhibition occurring at a LOEL of 0.53 mg/kg/day. The NOEL of 0.11 mg/kg/day will be used for risk assessment. An UF of 100 will be used.

5. CHRONIC OCCUPATIONAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)

For chronic occupational exposure, the two-year chronic feeding study in rats (Acc. No. 252501, 252502, 252503, 253346, 253372, 253373, 253374) was selected, based on systemic toxicity, neuropathology, and cholinesterase inhibition occurring at the LOEL of 0.21 mg/kg/day. The NOEL of 0.02 mg/kg/day will be used for risk assessment. An UF of 100 will be used.

6. INHALATION EXPOSURE:

For short or intermediate term inhalation exposure, the one year rat neurotoxicity study (MRID No.: 41853801, 44204501) was selected, based on neuropathology and cholinesterase inhibition occurring at a LOEL of 0.53 mg/kg/day. The NOEL of 0.11 mg/kg/day will be used for risk assessment. An UF of 100 will be used.

For long term inhalation exposure, the two-year chronic feeding study in rats (Acc. No. 252501, 252502, 252503, 253346, 253372, 253373, 253374) was selected, based on systemic toxicity, neuropathology, and cholinesterase inhibition occurring at the LOEL of 0.21 mg/kg/day. The NOEL of 0.02 mg/kg/day will be used for risk assessment. Due to high toxicity seen in an acute inhalation study, 100% absorption should be assumed. An UF of 100 will be used.